ORIGINAL ARTICLE

Adjunctive Middle Meningeal Artery Embolization for Subdural Hematoma

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ABSTRACT

BACKGROUND

Subacute and chronic subdural hematomas are common and frequently recur after surgical evacuation. The effect of adjunctive middle meningeal artery embolization on the risk of reoperation remains unclear.

METHODS

In a prospective, multicenter, interventional, adaptive-design trial, we randomly assigned patients with symptomatic subacute or chronic subdural hematoma with an indication for surgical evacuation to undergo middle meningeal artery embolization plus surgery (treatment group) or surgery alone (control group). The primary end point was hematoma recurrence or progression that led to repeat surgery within 90 days after the index treatment. The clinical secondary end point was deterioration of neurologic function at 90 days, which was assessed with the modified Rankin scale in a noninferiority analysis (margin for risk difference, 15 percentage points).

RESULTS

A total of 197 patients were randomly assigned to the treatment group and 203 to the control group. Surgery occurred before randomization in 136 of 400 patients (34.0%). Hematoma recurrence or progression leading to repeat surgery occurred in 8 patients (4.1%) in the treatment group, as compared with 23 patients (11.3%) in the control group (relative risk, 0.36; 95% confidence interval [CI], 0.11 to 0.80; P=0.008). Functional deterioration occurred in 11.9% of the patients in the treatment group and in 9.8% of those in the control group (risk difference, 2.1 percentage points; 95% CI, −4.8 to 8.9). Mortality at 90 days was 5.1% in the treatment group and 3.0% in the control group. By 30 days, serious adverse events related to the embolization procedure had occurred in 4 patients (2.0%) in the treatment group, including disabling stroke in 2 patients; no additional events had occurred by 180 days.

CONCLUSIONS

Among patients with symptomatic subacute or chronic subdural hematoma with an indication for surgical evacuation, middle meningeal artery embolization plus surgery was associated with a lower risk of hematoma recurrence or progression leading to reoperation than surgery alone. Further study is needed to evaluate the safety of middle meningeal artery embolization in the management of subdural hematoma. (Funded by Medtronic; EMBOLISE ClinicalTrials.gov number, NCT04402632.)

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Surgical evacuation for the treatment of subacute or chronic subdural hematoma is frequently indicated and is projected to be the most common cranial neurosurgical procedure by 2030.[1,2] An inflammatory response to subacute or chronic subdural hematoma produces vascularized membranes that can prevent resorption and contribute to recurrence.[3] Age-related frailty and coexisting conditions add to surgical risks.[4] Recurrence after surgery occurs in 8 to 20% of patients,[5-10] and surgical complications occur in 3 to 28%.[11-13] Retreatment can lead to clinical deterioration and poor clinical outcomes[14] and has been associated with longer hospital stays,[15] as well as increased morbidity, mortality, and costs.[16-18]

Middle meningeal artery embolization is a nonsurgical procedure aimed at reducing the blood supply to inflamed dural vascular membranes.[19] Multiple preliminary studies suggest that middle meningeal artery embolization reduces the risk of hematoma recurrence.[14,19-40] The radiopaque, injectable Onyx liquid embolic system (Medtronic) was approved in the United States in 2005 for presurgical embolization of arteriovenous malformations in the brain. The Embolization of the Middle Meningeal Artery with Onyx Liquid Embolic System in the Treatment of Subacute and Chronic Subdural Hematoma (EMBOLISE) trial evaluated whether middle meningeal artery embolization with the embolic agent Onyx, performed as an adjunct to standard care, would result in a lower risk of reoperation and concomitant poor outcomes than standard care alone. Here, we present the results for middle meningeal artery embolization plus surgery as compared with surgery alone in patients with a large subdural hematoma with neurologic symptoms and an indication for surgical management.

METHODS

TRIAL DESIGN AND OVERSIGHT

We conducted a prospective, multicenter, interventional, open-label, adaptive-design, randomized, controlled trial that enrolled patients in whom surgical evacuation as the primary treatment for subdural hematoma was indicated. Complete details about the trial design, statistical analyses, trial oversight, and procedures are provided with the protocol, which is available with the full text of this article at NEJM.org.

A multidisciplinary steering committee led the design and oversight of the trial. An independent data and safety monitoring committee oversaw safety by reviewing adverse events and serious adverse events, safety considerations, data integrity, and adaptive enrollment decisions. Safety events were adjudicated by an independent clinical events committee. An independent core laboratory (Eppdata) performed imaging analyses. The Viz Recruit platform (Viz.ai) supported enrollment at 20 trial sites.

The sponsor (Medtronic) funded the trial; gathered the data; conducted data monitoring; provided operational support to the trial sites, steering committee, core laboratory, clinical events committee, and data and safety monitoring committee; and assisted with the data analysis and review of the manuscript. The members of the steering committee signed confidentiality agreements and selected the trial sites in conjunction with the sponsor. The first, second, and last authors designed the trial, had complete discretion to submit the results for publication, and drafted and revised the manuscript. All the authors reviewed and contributed to the final version of the manuscript in accordance with the prespecified publication plan, had full access to the data, and vouch for the accuracy and completeness of the data. The trial was conducted in accordance with the principles of the Declaration of Helsinki. The trial protocol was approved by the institutional review board at each site. All the authors vouch for the fidelity of the trial to the protocol. All the patients were enrolled after written informed consent was obtained, with information provided about the trial design and processes, the possible risks and benefits, and the patients' rights to decline to participate and to leave the trial.

A Quick Take is available at NEJM.org

PATIENTS

Eligible patients 18 to 90 years of age who had computed tomographic (CT) evidence of subacute or chronic subdural hematoma were enrolled if the treating neurosurgeon determined that surgery was indicated and that at least one of the following criteria was met: neurologic symptoms (beyond headache, imbalance, and confusion), a focal motor deficit attributable to the subdural hematoma, a maximum thickness of the hematoma of more than 15 mm, or a midline shift of at least 5 mm. Patients were excluded if they

had a life expectancy of less than 1 year; if they had had a score on the modified Rankin scale, designed to assess functional independence, of 4 or 5 (scores range from 0 [no symptoms] to 6 [death]) before the hematoma developed; or if they had a prerandomization score on the Markwalder Grading Scale, designed to assess the severity of signs of subdural hematoma, of at least 3 (scores range from 0 to 4, with a score of 0 indicating normal status, a score of 3 stuporous or severe focal signs, and a score of 4 coma). Full enrollment criteria are provided in the protocol. Screening logs were not required.

TREATMENT

For the surgical procedure, either burr holes or craniotomy could be used according to the surgeon's discretion. Patients were randomly assigned in a 1:1 ratio to undergo middle meningeal artery embolization plus surgery (treatment group) or to undergo surgery alone (control group). Randomization was conducted in a central Web-based procedure with the use of a permuted-block randomization scheme, with stratification according to hematoma thickness (0 to 15 mm vs. >15 mm), Markwalder Grading Scale score (1 vs. 2), surgery type (burr hole vs. craniotomy), and use of antithrombotic agents (yes vs. no). Randomization occurred after the neurosurgeon determined that surgery was indicated or up to 72 hours after surgery was completed. Patients who were randomly assigned to the treatment group could undergo surgery either before or after the embolization procedure; middle meningeal artery embolization took place within 48 hours after randomization. No crossover, use of glucocorticoids for the treatment of subdural hematoma, or use of other embolic agents was allowed.

Middle meningeal artery embolization was performed with the use of biplane digital subtraction angiography. The catheter was inserted into the middle meningeal artery located on the same side as the subdural hematoma, and the embolic agent (Onyx) was injected on that side or on both sides according to the discretion of the physician. To ensure safe and adequate middle meningeal artery embolization, a principal investigator (the first or second author) evaluated images for the first three patients who underwent embolization at each trial site. Success was defined as successful target-vessel embolization with the embolic agent.

ADJUDICATION AND BLINDING PROCEDURES

At each trial site, independent outcomes assessors (who had no access to the trial-group assignments, previous clinical evaluations, or imaging) evaluated the 90-day scores on the Markwalder Grading Scale, Medical Research Council scale for muscle strength, Glasgow Coma Scale, and modified Rankin scale in a blinded manner. The core laboratory independently evaluated imaging; the readers for CT images differed from those for angiographic images, but readers could not be unaware of the treatment received, given that the embolic agent used in this trial is radiopaque.

END POINTS

The primary end point as adjudicated by the clinical events committee was recurrence or progression of subdural hematoma that led to repeat surgery within 90 days after the index treatment. Recurrence was defined as the presence of imaging evidence of subdural hematoma with or without new or worsening symptoms. The number of days after the index treatment was counted from the date of the embolization procedure in the treatment group and from the date of the index surgical procedure in the control group, although patients in both groups underwent surgery. Repeat surgery within 90 days after the index treatment was considered to be the primary end-point event. Reoperation was done according to the physician's discretion. The clinical events committee determined whether the reoperation was for the target subdural hematoma. If the committee determined that there was a documented need for a surgical intervention for the treatment of hematoma recurrence or progression but the intervention could not be completed, the documented indication for repeat surgery could be considered the primary end-point event.

The clinical secondary end point was deterioration of neurologic function at 90 days, which was assessed with the modified Rankin scale in a noninferiority analysis (margin for risk difference, 15 percentage points). In patients with favorable function at baseline (a score of <3 on the modified Rankin scale), deterioration was defined as unfavorable function (a score of ≥3); in patients with unfavorable function at baseline (a score of ≥3), deterioration was defined as worsening of function (a score increase of ≥1 point). The score on the modified Rankin scale at presentation (i.e., the evaluation closest to the inter-

vention) served as the baseline value. For patients who died before the 90-day assessment, a score of 6 was used. In addition, there were four effectiveness secondary end points, which were evaluated in the following rank order: hospital readmissions within 90 days, followed by the changes in hematoma volume, hematoma thickness, and midline shift at 90 days according to assessment by the core laboratory.

Safety end points that were adjudicated by the clinical events committee included serious adverse events related to the embolic agent and serious adverse events related to middle meningeal artery embolization within 30 days and neurologic death and adverse events related to the embolic agent within 90 days and 180 days. Technical success was defined as identification of the embolic agent in the target vessel by the core laboratory.

STATISTICAL ANALYSIS

An initial sample size of 200 was determined on the basis of previous literature. At the prespecified interim analysis, the conditional power to show superiority of the treatment over the control (defined as a P value of <0.05) was 34% for the intention-to-treat population (below the prespecified boundary for futility of 37%) and was 72% for the modified intention-to-treat population (near the upper boundary for reestimation of the sample size). In the absence of safety concerns identified by the data and safety monitoring committee and with consideration of the conditional power of the modified intention-to-treat population, the sponsor increased the sample size to 400. The intention-to-treat population included all the enrolled patients who provided written informed consent and underwent randomization; this population was used for analysis of the primary and safety end points. The modified intention-to-treat population excluded patients who did not complete the assigned treatment.

Continuous variables were compared with the use of Student's t-test or Wilcoxon's rank-sum test. Categorical variables were compared with the use of Fisher's exact test. Primary end-point data for patients who missed the 90-day visit were imputed with the use of multiple imputation by fully conditional specification methods. The four prospectively specified and ordered effectiveness secondary end points were evaluated with the use of a fixed-sequence testing procedure to control for multiplicity (in accordance with guidance from the Food and Drug Administration[41]). The noninferiority analysis of the clinical secondary end point was performed with the use of a Farrington–Manning test (two-sided analysis with an alpha level of 0.05; noninferiority margin, 15 percentage points). Details are provided in the Supplementary Methods section in the Supplementary Appendix, available at NEJM.org.

Confidence intervals for the additional efficacy outcomes and safety outcomes were not adjusted for multiplicity and should not be used for statistical inference. Statistical analyses were performed with the use of SAS software, version 9.4 or higher (SAS Institute). Details of the statistical analyses in the intention-to-treat population are included in the statistical analysis plan (see pages 14 through 34 in the Supplementary Appendix).

RESULTS

ENROLLMENT AND PATIENT CHARACTERISTICS

From December 2020 through August 2023, a total of 400 patients underwent randomization at 39 centers in the United States. A total of 197 patients were randomly assigned to the treatment group and 203 to the control group (Fig. S1 in the Supplementary Appendix).

A total of 167 patients in the treatment group and 180 patients in the control group completed the 90-day clinical follow-up, with 53 patients (13.2%) overall being lost to follow-up. Primary end-point data were available for 173 patients in the treatment group and for 186 patients in the control group; 6 patients in each group underwent reoperation before 90 days and contributed to the end-point data despite missing the 90-day visit. Primary end-point data were imputed for 24 patients in the treatment group and for 17 in the control group.

The trial population was typical of patients presenting with subdural hematoma (Table S1). The demographic and clinical characteristics of the patients at baseline — including symptoms at presentation and imaging characteristics (Table 1), functional and neurologic status (Table S2), and coexisting conditions (Table S3) — were similar in the two trial groups. The mean age of the patients was 73 years in the treatment group and 71 years in the control group; the mean

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Treatment Group (N=197)	Control Group (N=203)
Age — yr	73.0±11.0	71.0±11.3
Male sex — no. (%)	143 (72.6)	149 (73.4)
Surgery before randomization — no./total no. (%)†	56/196 (28.6)	80/202 (39.6)
Symptoms at presentation — no. (%)‡		
Headaches	135 (68.5)	146 (71.9)
Gait instability	140 (71.1)	137 (67.5)
Limb weakness	115 (58.4)	117 (57.6)
Cognitive impairment	89 (45.2)	92 (45.3)
Focal neurologic deficit	68 (34.5)	86 (42.4)
Other	154 (78.2)	160 (78.8)
Antiplatelet or anticoagulant use — no. (%)§	75 (38.1)	79 (38.9)
Chronic or subacute subdural hematoma — no. (%)		
Chronic	115 (58.4)	116 (57.1)
Subacute	82 (41.6)	87 (42.9)
Target side of subdural hematoma — no. (%)		
Left	97 (49.2)	111 (54.7)
Right	100 (50.8)	92 (45.3)
Subdural hematoma on both sides — no. (%)	42 (21.3)	37 (18.2)
Hematoma volume at screening — ml	222.8±109.6	235.7±118.2
Hematoma thickness at screening — mm	21.6±6.3	21.4±6.2
Midline shift at screening — mm	7.9±3.6	8.6±4.1
Modified Rankin scale score — no. (%)¶		
<3	125 (63.5)	121 (59.6)
≥3	72 (36.5)	82 (40.4)

* Plus–minus values are means ±SD. The intention-to-treat population included all the patients who provided informed consent and underwent randomization to undergo middle meningeal artery embolization plus surgery (treatment group) or surgery alone (control group).
† One patient in each group withdrew consent after randomization and hence did not undergo surgery.
‡ If the clinical evaluation of symptoms was performed more than once before the intervention, the evaluation closest to the intervention is summarized. The category of "other" included a decreased level of consciousness, dizziness, double vision, isolated third-nerve palsy, limb numbness or tingling, memory loss, nausea or vomiting, seizures, and speech disturbance.
§ Antiplatelet or anticoagulant use included any use of an antiplatelet or anticoagulant agent after the initial onset of symptoms of subdural hematoma, as recorded in the clinical evaluation at the screening visit.
¶ Scores on the modified Rankin scale range from 0 (no symptoms) to 6 (death).

hematoma thickness was 21.6 mm and 21.4 mm, respectively; and the mean modified Rankin scale score was 2.2 and 2.3, respectively. A total of 28.6% of the patients in the treatment group and 39.6% of those in the control group underwent surgery before randomization. Burr-hole surgery was performed in 53.6% of the patients in the treatment group and in 51.0% of those in the control group, and craniotomy was performed in 46.4% and 49.0%, respectively (Table S4).

PROCEDURAL CHARACTERISTICS

Investigators reported successful middle meningeal artery embolization in 185 of 197 patients (93.9%). Owing to dangerous anatomical variants (i.e., variants associated with a high risk of complications), 10 patients did not undergo embolization and 1 other patient underwent embolization with coils alone. One patient withdrew before receiving treatment. Middle meningeal artery embolization was performed under

Table 2. Primary and Clinical Secondary End Points (Intention-to-Treat Population).

End Point	Treatment Group (N=197)	Control Group (N=203)	Treatment Effect (95% CI)*
Primary end point: recurrence or progression of subdural hematoma that led to repeat surgery within 90 days after the index treatment†			
Analysis performed with imputed data‡			
No. of patients with event	8	23	—
Percentage of patients (95% CI)§	4.1 (1.8 to 7.8)	11.3 (7.3 to 16.5)	—
Relative risk	—	—	0.36 (0.11 to 0.80)
P value	—	—	0.008
Analysis performed with observed data only			
No. of patients with event/total no.¶	8/182	21/190	—
Percentage of patients (95% CI)	4.4 (1.9 to 8.5)	11.1 (7.0 to 16.4)	—
Relative risk	—	—	0.40 (0.14 to 0.93)
P value	—	—	0.02
Clinical secondary end point: deterioration of neurologic function at 90 days‖			
No. of patients with event/total no.	21/177	18/184	—
Percentage of patients (95% CI)	11.9 (7.5 to 17.6)	9.8 (5.9 to 15.0)	—
Risk difference — percentage points	—	—	2.1 (−4.8 to 8.9)

* For the primary end-point analyses, the relative risk is shown with exact unconditional 95% confidence interval. For the analysis of the clinical secondary end point, the risk difference is shown with the 95% confidence interval. P values were calculated by means of Fisher's exact test.

† According to adjudication by the clinical events committee, a primary end-point event was considered to be either a surgical intervention or a documented indication for a surgical intervention (which could not be completed, regardless of reason) that was attributed to hematoma recurrence or progression and occurred within 90 days after the index treatment.

‡ Data were imputed for 24 patients in the treatment group (9 who died and 15 with missing data) and for 17 patients in the control group (4 who died and 13 with missing data). Information about the imputation methods is provided in the protocol.

§ The exact binomial Clopper–Pearson confidence interval was calculated.

¶ The denominators exclude patients who exited the trial before the 90-day visit for reasons other than death and did not have recurrence or progression of subdural hematoma leading to repeat surgery, as adjudicated by the clinical events committee, before exiting the trial.

‖ Deterioration in neurologic function at 90 days was defined as a score of 3 or more on the modified Rankin scale at 90 days among patients with a score of less than 3 at baseline or as a score increase of at least 1 point at 90 days among patients with a score of 3 or more at baseline. The clinical secondary end point was assessed in a noninferiority analysis (margin for risk difference, 15 percentage points).

general anesthesia in 155 of 196 patients (79.1%) and was performed after surgery in 78 of 185 patients (42.2%). Details regarding the characteristics of the embolization procedures are provided in Table S5.

Successful embolization as adjudicated by the core laboratory was observed in all 185 patients (100%) in whom the procedure was attempted, and reflux to a nontarget vessel (e.g., petrosal or collaterals) was observed in 3 patients (1.6%). Proximal occlusion of the middle meningeal artery was observed in 92 of 185 patients (49.7%), and distal occlusion of the artery in 91 patients (49.2%); the site of the occlusion could not be determined in 2 patients (1.1%) (Table S6).

PRIMARY EFFICACY OUTCOME

In the intention-to-treat population, 8 of 197 patients (4.1%; 95% confidence interval [CI], 1.8 to 7.8) in the treatment group underwent reoperation for hematoma recurrence or progression, as compared with 23 of 203 (11.3%; 95% CI, 7.3 to 16.5) in the control group (relative risk, 0.36; 95% CI, 0.11 to 0.80; P=0.008) (Table 2). The number needed to treat to avoid one reoperation was 14. Results in the modified intention-to-treat population were similar to those in the intention-to-treat population (Table S7). Details of management decisions for each primary end-point event are provided in Table S8. For 3 patients in the control group who had hematoma recurrence or progression, retreatment was performed

in a manner not specified in the protocol (with middle meningeal artery embolization only). Because surgical retreatment was not performed, these patients did not contribute to the primary end-point data. After retreatment with middle meningeal artery embolization, none of these patients had progression or underwent surgery. Two patients in the treatment group who met the primary end point had not undergone embolization because they had dangerous anatomical variants.

SECONDARY EFFICACY OUTCOMES

The results for the clinical secondary end point, functional deterioration, were similar in the two trial groups. A total of 21 of 177 patients (11.9%; 95% CI, 7.5 to 17.6) in the treatment group and 18 of 184 patients (9.8%; 95% CI, 5.9 to 15.0) in the control group had functional deterioration (risk difference, 2.1 percentage points; 95% CI, −4.8 to 8.9) (Table 2). The results met the prespecified threshold for noninferiority (15 percentage points) but not for superiority. The mean (±SD) change in the modified Rankin scale score was −0.9±1.7 points in the treatment group and −1.1±1.5 points in the control group. Additional results regarding modified Rankin scale scores are provided in Table S9.

The results for the first effectiveness secondary end point, the mean number of hospital readmissions within 90 days, were similar in the two groups: 0.3±0.6 (range, 0 to 3) in the treatment group and 0.3±0.5 (range, 0 to 3) in the control group (P=0.60). Therefore, in accordance with the fixed-sequence design to control the type I error inflation with multiple comparisons, statistical testing was not conducted for the three remaining effectiveness secondary end points (changes in the hematoma volume, hematoma thickness, and midline shift at 90 days) (Table S10).

SAFETY OUTCOMES

By 90 days, 10 of 197 patients (5.1%) in the treatment group and 6 of 203 patients (3.0%) in the control group had died (relative risk, 1.72; 95% CI, 0.62 to 5.54; P=0.32). Neurologic death as adjudicated by the clinical events committee had occurred in 9 patients (4.6%) in the treatment group and in 4 patients (2.0%) in the control group (relative risk, 2.32; 95% CI, 0.73 to 15.12; P=0.17). Most neurologic deaths were related to the underlying subdural hematoma (in 8 patients [4.1%] in the treatment group and in 2 patients [1.0%] in the control group, P=0.06). The remaining neurologic deaths were related to surgery (in 1 patient [0.5%] in the treatment group and in 2 patients [1.0%] in the control group, P>0.99). The clinical events committee reviewed each death, identified the adverse event that most accurately represented the cause of death, and assessed the relationship to the procedure or device. On the basis of this assessment, none of the deaths in the treatment group were deemed to be related to middle meningeal artery embolization or the embolic agent. Patients who died were older (mean age, >80 years) with substantial coexisting conditions (Table S11).

By 30 days, serious adverse events that were adjudicated by the clinical events committee to be related to middle meningeal artery embolization alone had occurred in 4 patients (2.0%) in the treatment group, including disabling stroke in 2 patients (Table 3). By 180 days, no additional serious adverse events related to the embolization procedure had occurred. Serious adverse events at 30 days were related to surgery in fewer patients in the treatment group than in the control group (32 patients [16.2%] and 44 patients [21.7%], respectively; P=0.20). The incidence of stroke at 90 days was similar in the two groups, with stroke occurring in 4 patients (2.0%) in the treatment group and in 3 patients (1.5%) in the control group (P=0.72). None of the patients with serious adverse events had any reflux-related complications, and no cases of ipsilateral vision loss occurred in the treatment group. Table S12 provides a summary of all the adverse events as adjudicated by the clinical events committee.

DISCUSSION

This randomized, controlled trial involving patients with symptomatic subacute or chronic subdural hematoma and an indication for surgical evacuation showed a significantly lower risk of reoperation and a similar risk of deterioration in neurologic function after middle meningeal artery embolization plus surgery than after surgery alone. The 90-day mortality appeared to be higher in the treatment group than in the control group (5.1% vs. 3.0%), but the difference was not attributed by independent assessors to the embolic agent or to the embolization procedure.

Previous studies reported embolization with the use of coils, Onyx, polyvinyl alcohol particles, and *N*-butyl-2-cyanoacrylate. Onyx has a history

Table 3. Safety End Points (Intention-to-Treat Population).*

End Point	Treatment Group (N=197)	Control Group (N=203)	Relative Risk (95% CI)	P Value†
	no. of patients with event (%)			
Serious adverse events at 30 days				
Related to surgical procedure‡	32 (16.2)	44 (21.7)	0.75 (0.49–1.14)	0.20
Related to middle meningeal artery embolization alone	4 (2.0)	—	—	—
Adverse events related to embolic agent at 180 days	0	—	—	—
Neurologic death				
At 90 days	9 (4.6)	4 (2.0)	2.32 (0.73–15.12)	0.17
Related to subdural hematoma	8 (4.1)	2 (1.0)	4.12 (0.98–34.45)	0.06
Related to embolic agent	0	—	—	—
Related to middle meningeal artery embolization alone	0	—	—	—
Related to surgical procedure	1 (0.5)	2 (1.0)	0.52 (0.02–5.73)	>0.99
At 180 days	11 (5.6)	5 (2.5)	2.27 (0.80–6.41)	0.13
Related to subdural hematoma	10 (5.1)	3 (1.5)	3.43 (0.96–12.30)	0.05
Related to embolic agent	0	—	—	—
Related to middle meningeal artery embolization alone	0	—	—	—
Related to surgical procedure	1 (0.5)	2 (1.0)	0.52 (0.05–5.64)	>0.99
Death from any cause at 90 days	10 (5.1)	6 (3.0)	1.72 (0.62–5.54)	0.32
Stroke at 90 days	4 (2.0)	3 (1.5)	1.37 (0.30–11.18)	0.72
Related to embolic agent	0	—	—	—
Related to middle meningeal artery embolization alone	2 (1.0)	—	—	—
Related to surgical procedure	1 (0.5)	1 (0.5)	1.03 (0.03–34.44)	>0.99
Not related to surgical procedure	1 (0.5)	2 (1.0)	0.51 (0.02–5.73)	>0.99

* The safety end points listed here were adjudicated by the clinical events committee. In the treatment group, events related to the surgical procedure included events related to the embolization procedure. The number of days to events related to the surgical procedure was counted from the date of the index surgical procedure to the start date of the event as reported by the trial site. The number of days to events related to the embolization procedure was counted from the date of the embolization procedure to the start date of the event as reported by the trial site. The number of days to death was counted from the date of randomization to the date of death as reported by the trial site. The number of days to stroke was counted from the date of time 0 to the start date of the event as reported by the trial site, with time 0 defined as the time point that computed tomographic or magnetic resonance imaging data were obtained within 30 hours after all interventions (surgery or embolization).

† P values were calculated by Fisher's exact test.

‡ In the treatment group, 48 events occurred in 32 patients; in the control group, 55 events occurred in 44 patients.

of operator familiarity and ease of visualization. This embolic agent was chosen as the sole agent in this trial sponsored by Medtronic. Only three patients had reflux into the petrosal or transosseous branches; none of these patients had any reflux-related complications.

The primary end point was selected because reoperation is associated with increases in morbidity and mortality, as well as with poor health-economic outcomes.[14-18] Previous trials have shown conflicting results regarding adverse events and reoperation.[8] In this trial, the 30-day incidence of serious adverse events that were related to middle meningeal artery embolization alone was 2.0%. No significant between-group difference was observed with regard to the risk of stroke (2.0% in the treatment group vs. 1.5% in the control group, P=0.72) or neurologic death (4.6% vs. 2.0%, P=0.17). Although the between-group differences could be important, the trial was not powered for these end points.

In the treatment group, the clinical events committee adjudicated two strokes as being related to the embolization procedure. The first case involved ipsilateral embolic infarcts, which were probably due to catheter manipulation. The

second case involved infarcts in the vertebrobasilar system, which were probably related to underlying atherosclerosis, given that these vessels were not directly catheterized. Because causality by the embolization procedure could not be ruled out, the clinical events committee adjudicated the stroke as being possibly related. The incidence of these complications is consistent with observed outcomes after neuroendovascular procedures in older patients,[42] although the cited study did not include middle meningeal artery embolization.

The EMBOLISE trial was an open-label trial with a primary end point that was based on surgeon judgment and was thus prone to bias. Treating neurosurgeons were empowered to consider imaging findings and symptoms when deciding when to reoperate, an approach that is consistent with current clinical practice. This dichotomous end point is subject to bias in favor of the treatment group. Bias-mitigation measures included the provision of comprehensive guidance to enrolling centers, a requirement of documentation in the case-report form at each follow-up or unscheduled visit about the retreatment decision and rationale, and the inclusion of quantitative secondary outcomes to assess neurologic functional and imaging deterioration with the use of standardized scales and metrics for objectivity. In addition, there was a risk of bias by the core laboratory and the clinical events committee, given that imaging could not be blinded owing to the radiopacity of the embolic agent used in this trial.

In the hierarchical analysis of effectiveness secondary end points, the results for the first end point (hospital readmissions) were not significant, so the additional outcomes (changes in hematoma volume, hematoma thickness, and midline shift) could not be evaluated for comparative statistical inferences. Some heterogeneity exists in the degree of embolization achieved; additional analyses are warranted to evaluate how this factor interacts with outcomes. The risk of retreatment in the trial might have been higher if high-risk patients — such as patients with a modified Rankin scale score of 4 or 5, a Markwalder Grading Scale score of 3 or higher, leukemia or renal insufficiency, or continued use of antithrombotic agents — had been included. Finally, the loss to follow-up was substantial (13.2% of the patients), a situation that was probably due to the predominantly older population of patients and to the trial onset during the coronavirus disease 2019 pandemic.

This trial showed a significantly lower risk of reoperation among patients who had undergone middle meningeal artery embolization as an adjunct to surgery for subacute or chronic subdural hematoma than among those who had undergone surgery alone. The risk of functional deterioration was similar in the two trial groups; mortality was numerically higher in the treatment group than in the control group. Further study with larger sample sizes is necessary for the efficacy and safety of middle meningeal artery embolization for the management of subdural hematoma to be evaluated fully.

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APPENDIX

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